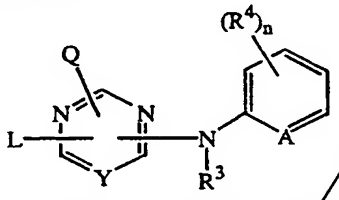
Claims

1. A particle consisting of a solid dispersion comprising
(a) a compound of formula



(I-A)

a N-oxide, a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof, wherein
Y is CR^5 or N;
A is CH, CR^4 or N;
n is 0, 1, 2, 3 or 4;
Q is $-NR^1R^2$ or when Y is CR^5 then Q may also be hydrogen;
R^1 and R^2 are each independently selected from hydrogen, hydroxy, C_{1-12}alkyl, C_{1-12}alkyloxy, C_{1-12}alkylcarbonyl, C_{1-12}alkyloxycarbonyl, aryl, amino, mono- or di(C_{1-12}alkyl)amino, mono- or di(C_{1-12}alkyl)aminocarbonyl wherein each of the aforementioned C_{1-12}alkyl groups may optionally and each individually be substituted with one or two substituents each independently selected from hydroxy, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyloxy, carboxyl, C_{1-6}alkyloxycarbonyl, cyano, amino, imino, aminocarbonyl, aminocarbonylamino, mono- or di(C_{1-6}alkyl)amino, aryl and Het; or
R^1 and R^2 taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C_{1-12}alkyl)aminoC_{1-4}alkylidene;
R^3 is hydrogen, aryl, C_{1-6}alkylcarbonyl, C_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyl substituted with C_{1-6}alkyloxycarbonyl; and
each R^4 independently is hydroxy, halo, C_{1-6}alkyl, C_{1-6}alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalomethyloxy, or when Y is CR^5 then R^4 may also represent C_{1-6}alkyl substituted with cyano or aminocarbonyl;
R^5 is hydrogen or C_{1-4}alkyl;
L is $-X^1-R^6$ or $-X^2$-Alk-R^7 wherein
R^6 and R^7 each independently are phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, formyl, cyano, nitro, amino, and trifluoromethyl; or when Y is CR^5 then R^6 and R^7 may also be selected from phenyl substituted with one, two, three, four or five substituents each independently selected from aminocarbonyl, trihalomethyloxy

and trihalomethyl; or when Y is N then R^6 and R^7 may also be selected from indanyl or indolyl, each of said indanyl or indolyl may be substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, formyl, cyano, nitro, amino, and trifluoromethyl;

X^1 and X^2 are each independently $-NR^3-$, -NH-NH-, -N=N-, -O-, -S-, -S(=O)- or $-S(=O)_2-$;

Alk is C_{1-4}alkanediyl; or

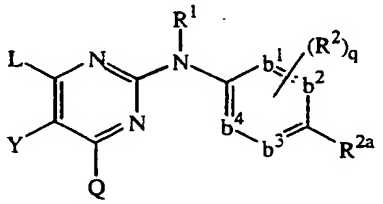
when Y is CR^5 then L may also be selected from C_{1-10}alkyl, C_{3-10}alkenyl, C_{3-10}alkynyl, C_{3-7}cycloalkyl, or C_{1-10}alkyl substituted with one or two substituents independently selected from C_{3-7}cycloalkyl, indanyl, indolyl and phenyl, wherein said phenyl, indanyl and indolyl may be substituted with one, two, three, four or where possible five substituents each independently selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, cyano, aminocarbonyl, C_{1-6}alkyloxycarbonyl, formyl, nitro, amino, trihalomethyl, trihalomethyloxy and C_{1-6}alkylcarbonyl;

aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy, cyano, nitro and trifluoromethyl;

Het is an aliphatic or aromatic heterocyclic radical; said aliphatic heterocyclic radical is selected from pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl and tetrahydrothienyl wherein each of said aliphatic heterocyclic radical may optionally be substituted with an oxo group; and said aromatic heterocyclic radical is selected from pyrrolyl, furanyl, thienyl, pyridyl, pyrimidinyl, pyrazinyl and pyridazinyl wherein each of said aromatic heterocyclic radical may optionally be substituted with hydroxy;

or

a compound of formula



(I-B)

the *N*-oxides, the pharmaceutically acceptable addition salts, quaternary amines and the stereochemically isomeric forms thereof, wherein

$-b^1=b^2-C(R^{2a})=b^3-b^4=$ represents a bivalent radical of formula

$-CH=CH-C(R^{2a})=CH-CH=$ (b-1);

$-N=CH-C(R^{2a})=CH-CH=$ (b-2);

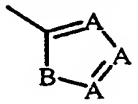
-CH=N-C(R^{2a})=CH-CH= (b-3);
-N=CH-C(R^{2a})=N-CH= (b-4);
-N=CH-C(R^{2a})=CH-N= (b-5);
-CH=N-C(R^{2a})=N-CH= (b-6);
-N=N-C(R^{2a})=CH-CH= (b-7);

q is 0, 1, 2; or where possible q is 3 or 4;

R^1 is hydrogen, aryl, formyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyl substituted with formyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl;

R^{2a} is cyano, aminocarbonyl, mono- or di(methyl)aminocarbonyl, C_{1-6}alkyl substituted with cyano, aminocarbonyl or mono- or di(methyl)aminocarbonyl, C_{2-6}alkenyl substituted with cyano, or C_{2-6}alkynyl substituted with cyano;

each R^2 independently is hydroxy, halo, C_{1-6}alkyl optionally substituted with cyano or -C(=O)R^6, C_{3-7}cycloalkyl, C_{2-6}alkenyl optionally substituted with one or more halogen atoms or cyano, C_{2-6}alkynyl optionally substituted with one or more halogen atoms or cyano, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C_{1-6}alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, -S(=O)$_p$$R^6$, -NH-S(=O)$_p$$R^6$, -C(=O)$R^6$, -NHC(=O)H, -C(=O)$NHNH_2$, -NHC(=O)$R^6$, -C(=NH)$R^6$ or a radical of formula


(c)

wherein each A independently is N, CH or CR^6;

B is NH, O, S or NR^6;

p is 1 or 2; and

R^6 is methyl, amino, mono- or dimethylamino or polyhalomethyl;

L is C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{3-7}cycloalkyl, whereby each of said aliphatic group may be substituted with one or two substituents independently selected from

* C_{3-7}cycloalkyl,
* indolyl or isoindolyl, each optionally substituted with one, two, three or four substituents each independently selected from halo, C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, cyano, aminocarbonyl, nitro, amino, polyhalomethyl, polyhalomethyloxy and C_{1-6}alkylcarbonyl,
* phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R^2; or

L is -X-R^3 wherein

R^3 is phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R^2; and

X is $-NR^1-$, -NH-NH-, -N=N-, -O-, -C(=O)-, -CHOH-, -S-, -S(=O)- or $-S(=O)_2-$;

Q represents hydrogen, C_{1-6}alkyl, halo, polyhaloC_{1-6}alkyl or $-NR^4R^5$; and

R^4 and R^5 are each independently selected from hydrogen, hydroxy, C_{1-12}alkyl, C_{1-12}alkyloxy, C_{1-12}alkylcarbonyl, C_{1-12}alkyloxycarbonyl, aryl, amino, mono- or di(C_{1-12}alkyl)amino, mono- or di(C_{1-12}alkyl)aminocarbonyl wherein each of the aforementioned C_{1-12}alkyl groups may optionally and each individually be substituted with one or two substituents each independently selected from hydroxy, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyloxy, carboxyl, C_{1-6}alkyloxycarbonyl, cyano, amino, imino, mono- or di(C_{1-6}alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, $-S(=O)_pR^6$, $-NH-S(=O)_pR^6$, $-C(=O)R^6$, -NHC(=O)H, $-C(=O)NHNH_2$, $-NHC(=O)R^6$, $-C(=NH)R^6$, aryl and Het; or

R^4 and R^5 taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C_{1-12}alkyl)aminoC_{1-4}alkylidene;

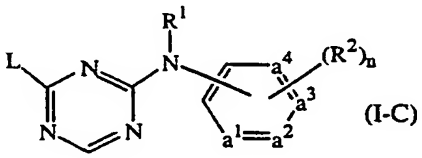
Y represents hydroxy, halo, C_{3-7}cycloalkyl, C_{2-6}alkenyl optionally substituted with one or more halogen atoms, C_{2-6}alkynyl optionally substituted with one or more halogen atoms, C_{1-6}alkyl substituted with cyano or $-C(=O)R^6$, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C_{1-6}alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, $-S(=O)_pR^6$, $-NH-S(=O)_pR^6$, $-C(=O)R^6$, -NHC(=O)H, $-C(=O)NHNH_2$, $-NHC(=O)R^6$, $-C(=NH)R^6$ or aryl;

aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{1-6}alkyloxy, cyano, nitro, polyhaloC_{1-6}alkyl and polyhaloC_{1-6}alkyloxy;

Het is an aliphatic or aromatic heterocyclic radical; said aliphatic heterocyclic radical is selected from pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl and tetrahydrothienyl wherein each of said aliphatic heterocyclic radical may optionally be substituted with an oxo group; and said aromatic heterocyclic radical is selected from pyrrolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl wherein each of said aromatic heterocyclic radical may optionally be substituted with hydroxy;

or

a compound of formula



(I-C)

the *N*-oxides, the pharmaceutically acceptable addition salts, quaternary amines and the stereochemically isomeric forms thereof, wherein

$-a^1=a^2-a^3=a^4-$ represents a bivalent radical of formula

-CH=CH-CH=CH- (a-1);

-N=CH-CH=CH- (a-2);

-N=CH-N=CH- (a-3);

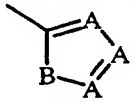
-N=CH-CH=N- (a-4);

-N=N-CH=CH- (a-5);

n is 0, 1, 2, 3 or 4; and in case $-a^1=a^2-a^3=a^4-$ is (a-1), then n may also be 5;

R^1 is hydrogen, aryl, formyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyl substituted with formyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl; and

each R^2 independently is hydroxy, halo, C_{1-6}alkyl optionally substituted with cyano or $-C(=O)R^4$, C_{3-7}cycloalkyl, C_{2-6}alkenyl optionally substituted with one or more halogen atoms or cyano, C_{2-6}alkynyl optionally substituted with one or more halogen atoms or cyano, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C_{1-6}alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, $-S(=O)_pR^4$, $-NH-S(=O)_pR^4$, $-C(=O)R^4$, $-NHC(=O)H$, $-C(=O)NHNH_2$, $-NHC(=O)R^4$, $-C(=NH)R^4$ or a radical of formula



(c)

wherein each A independently is N, CH or CR^4;

B is NH, O, S or NR^4;

p is 1 or 2; and

R^4 is methyl, amino, mono- or dimethylamino or polyhalomethyl;

L is C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{3-7}cycloalkyl, whereby each of said aliphatic group may be substituted with one or two substituents independently selected from

* C_{3-7}cycloalkyl,
* indolyl or isoindolyl, each optionally substituted with one, two, three or four substituents each independently selected from halo, C_{1-6}alkyl, hydroxy,

C_{1-6}alkyloxy, cyano, aminocarbonyl, nitro, amino, polyhalomethyl, polyhalomethyloxy and C_{1-6}alkylcarbonyl,

* phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R^2; or

L is -X-R^3 wherein

R^3 is phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R^2; and

X is -NR^1-, -NH-NH-, -N=N-, -O-, -C(=O)-, -CHOH-, -S-, -S(=O)- or -$S(=O)_2$-;

aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{1-6}alkyloxy, cyano, nitro, polyhaloC_{1-6}alkyl and polyhaloC_{1-6}alkyloxy;

with the proviso that compounds wherein

* L is C_{1-3}alkyl; R^1 is selected from hydrogen, ethyl and methyl; -a^1=a^2-a^3=a^4- represents a bivalent radical of formula (a-1); n is 0 or1 and R^2 is selected from fluoro, chloro, methyl, trifluoromethyl, ethyloxy and nitro; or
* L is -X-R^3, X is -NH-; R^1 is hydrogen; -a^1=a^2-a^3=a^4- represents a bivalent radical of formula (a-1); n is 0 or1 and R^2 is selected from chloro, methyl, methyloxy, cyano, amino and nitro and R^3 is phenyl, optionally substituted with one substituent selected from chloro, methyl, methyloxy, cyano, amino and nitro;

and the compounds

* *N,N'*-dipyridinyl-(1,3,5)-triazine-2,4-diamine;
* (4-chloro-phenyl)-(4(1-(4-isobutyl-phenyl)-ethyl)-(1,3,5) triazin-2-yl)-amine

are not included;

and

(b) one or more pharmaceutically acceptable water-soluble polymers.

2. A particle according to claim 1 having a particle size of less than 1500 μm.

3. A particle according to claim 1 or 2 wherein the compound of formula (I-A), (I-B) or (I-C) is in a non-crystalline phase.

4. A particle according to claim 3 wherein the solid dispersion is in the form of a solid solution comprising (a) and (b), or in the form of a dispersion wherein amorphous or

microcrystalline (a) or amorphous or microcrystalline (b) is dispersed more or less evenly in a solid solution comprising (a) and (b).

5. A particle according to the preceding claims wherein the compound of formula (I-A), (I-B) or (I-C) is 4-[[4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile 4-[[4-amino-5-bromo-6-(4-cyano-2,6-dimethylphenyloxy)-2-pyrimidinyl]amino]benzonitrile (R165335), 4-[[4-amino-5-chloro-6-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile (, 4-[[5-chloro-4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile (4-[[5-bromo-4-(4-cyano-2,6-dimethylphenoxy)-2-pyrimidinyl]amino]benzonitrile (4-[[4-amino-5-chloro-6-[(4-cyano-2,6-dimethylphenyl)amino]-2-pyrimidinyl]amino]-benzonitrile (4-[[5-bromo-6-[(4-cyano-2,6-dimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile (4-[[4-amino-5-chloro-6-(4-cyano-2,6-dimethylphenyloxy)-2-pyrimidinyl]amino]benzonitrile (4-[[2-[(cyanophenyl)amino]-4-pyrimidinyl]amino]-3,5-dimethylbenzonitrile (or 4-[[4-[(2,4,6-trimethylphenyl)amino]-1,3,5-triazin-2-yl]amino]benzonitrile .

6. A particle according to the preceding claims wherein the compound of formula (I-A) is 4-[[4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile .

7. A particle according to the preceding claims wherein the water-soluble polymer is a polymer that has an apparent viscosity of 1 to 5000 mPa.s when dissolved at 20°C in an aqueous solution at 2 % (w/v).

8. A particle according to claim 7 wherein the water-soluble polymer is selected from the group comprising
   - alkylcelluloses such as methylcellulose,
   - hydroxyalkylcelluloses such as hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and hydroxybutylcellulose,
   - hydroxyalkyl alkylcelluloses such as hydroxyethyl methylcellulose and hydroxypropyl methylcellulose,
   - carboxyalkylcelluloses such as carboxymethylcellulose,
   - alkali metal salts of carboxyalkylcelluloses such as sodium carboxymethyl-cellulose,
   - carboxyalkylalkylcelluloses such as carboxymethylethylcellulose,
   - carboxyalkylcellulose esters,
   - starches,

- pectines such as sodium carboxymethylamylopectine,
- chitin derivates such as chitosan,
- di-, oligo- or polysaccharides such as trehalose, cyclodextrins or a derivative thereof, alginic acid, alkali metal and ammonium salts thereof, carrageenans, galactomannans, tragacanth, agar-agar, gummi arabicum, guar gummi and xanthan gummi,
- polyacrylic acids and the salts thereof,
- polymethacrylic acids, the salts and esters thereof, methacrylate copolymers,
- polyvinylalcohol,
- polyalkylene oxides such as polyethylene oxide and polypropylene oxide and copolymers of ethylene oxide and propylene oxide.

9. A particle according to claim 8 wherein the water-soluble polymer is hydroxypropyl methylcellulose HPMC 2910 5 mPa.s.

10. A particle according to claim 9 wherein the weight-by-weight ratio of (a) : (b) is in the range of 1 : 1 to 1 : 899.

11. A particle according to any one of the preceding claims obtainable by melt-extrusion of the components and grinding, and optionally sieving.

12. A particle according to any one of the previous claims consisting of a solid solution comprising two parts by weight of a compound of formula (I-A), (I-B) or (I-C) and three parts by weight of hydroxypropyl methylcellulose HPMC 2910 5 mPa.s, obtainable by blending said components, extruding the blend at a temperature in the range of 20°C - 300°C, grinding the extrudate, and optionally sieving the thus obtained particles.

13. A particle according to the preceding claims further comprising one or more pharmaceutically acceptable excipients.

14. A pharmaceutical dosage form comprising a therapeutically effective amount of particles as claimed in any one of the preceding claims.

15. A dosage form according to claim 14 adapted for oral administration shaped as a tablet.

16. A dosage form according to claim 15 for immediate release of a compound of formula (I-A), (I-B) or (I-C) upon oral ingestion wherein said particles are homogeneously distributed throughout a mixture of a diluent and a disintegrant.

17. A dosage form according to claim 15 or 16 surrounded by a film-coat comprising a film-forming polymer, a plasticizer and optionally a pigment.

18. A dosage form according to claim 16 wherein the diluent is a spray-dried mixture of lactose monohydrate and microcrystalline cellulose (75 : 25), and the disintegrant is crospovidone or croscarmellose.

19. A dosage form according to any one of claims 14 to 18 wherein the weight of said particles is at least 40 % of the total weight of the dosage form.

20. A process of preparing particles as claimed in any one of claims 1 to 13 characterized by blending the components, extruding said blend at a temperature in the range of 20 - 300 °C, grinding the extrudate, and optionally sieving the particles.

21. A process of preparing a pharmaceutical dosage form as claimed in any one of claims 14 to 18 characterized by blending a therapeutically effective amount of particles as claimed in any one of claims 1 to 13 with pharmaceutically acceptable excipients and compressing said blend into tablets or filling said blend in capsules.

22. Particles according to any one of claims 1 to 13 for use in preparing a pharmaceutical dosage form for oral administration to a mammal suffering from a viral infection, wherein a single such dosage form can be administered once daily to said mammal.

23. Use of particles according to any one of claims 1 to 13 for the preparation of a pharmaceutical dosage form for oral administration to a mammal suffering from a viral infection, wherein a single such dosage form can be administered once daily to said mammal.

24. A pharmaceutical package suitable for commercial sale comprising a container, an oral dosage form of a compound of formula (I-A), (I-B) or (I-C) as claimed in any one of claims 14 to 19, and associated with said package written matter.